Chronic Fatigue Syndrome: Pathophysiology and Treatment

PA Number: PA-05-030

Part I Overview Information

Department of Health and Human Services

Participating Organizations
National Institutes of Health (NIH), (http://www.nih.gov)

Components of Participating Organizations
Office of Research on Women's Health (ORWH), (http://www4.od.nih.gov/orwh/)
Office of Dietary Supplements (ODS), (http://ods.od.nih.gov/index.aspx)
Office of Behavioral and Social Science Research (OBSSR), (http://obssr.od.nih.gov/)
National Institute on Alcohol Abuse and Alcoholism (NIAAA), (http://www.niaaa.nih.gov/)
National Institute of Allergy and Infectious Disease NIAID), (http://www.niaid.nih.gov/)
National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), (http://www.niams.nih.gov/)
National Institute of Child Health and Human Development (NICHD), (http://www.nichd.nih.gov/)
National Heart, Lung and Blood Institute (NHLBI), (http://www.nhlbi.nih.gov/)
National Institute of Environmental Health Sciences NIEHS), (http://www.niehs.nih.gov/)
National Institute of Nursing Research (NINR), (http://ninr.nih.gov/ninr/)
National Institute of Neurological Disorders and Stroke (NINDS), (http://www.ninds.nih.gov/)
National Institute of Dental and Craniofacial Research (NIDCR), (http://www.nidcr.nih.gov/)
National Institute on Aging (NIA), (http://www.nia.nih.gov/)

Announcement Type
This is a reissue of PA-02-034, which was previously released May 15, 1998

Catalog of Federal Domestic Assistance Number(s)
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Key Dates
Release Date: December 20, 2004
ApplicationReceipt Dates: http://grants.nih.gov/grants/funding/submissionschedule.htm
Peer Review Date(s): http://grants.nih.gov/grants/funding/submissionschedule.htm
Council Review Date(s): http://grants.nih.gov/grants/funding/submissionschedule.htm
Earliest Anticipated Start Date(s): http://grants.nih.gov/grants/funding/submissionschedule.htm
Expiration Date: November 2, 2007

Due Dates for E.O. 12372
Not applicable.

Executive Summary

The Office of Research on Women's Health (ORWH) and cosponsoring Institutes and Offices (IC) of the National Institutes of Health (NIH) invite submission of investigator-initiated research grant applications to support research on the epidemiology, diagnosis, pathophysiology, and treatment of chronic fatigue syndrome (CFS) in diverse groups and across the life span.

The total amount to be awarded and the anticipated number of individual awards depend upon the number of meritorious applications received and reviewed.

This PA will use the NIH R01, R21 and R03 mechanisms. Organizations that are eligible for this program include domestic non-profit organizations; public or private institutions, such as universities, colleges, hospitals, and laboratories; units of state and local governments; and eligible agencies of the Federal government.

There is no specific eligibility requirement for individuals to become Principal Investigators (PI); refer to eligibility information in Section III 1B. Applications must be prepared using the PHS 398 application form which can be downloaded at http://grants.nih.gov/grants/funding/phs398/phs398.html.

There is no limit to the number of applications an applicant may submit under this announcement.

Telecommunications for the hearing impaired: TTY 301 451-0088.

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Part II - Full Text of Announcement

Section I. Funding Opportunity Description

1. Research Objectives

The Office of Research on Women's Health (ORWH) and co-sponsoring Institutes and Offices (ICs) of the National Institutes of Health (NIH) invite submission of investigator-initiated research grant applications to support research on the epidemiology, diagnosis, pathophysiology, and treatment of chronic fatigue syndrome (CFS) in diverse groups and across the life span. Applications that address gaps in our understanding of the environmental and biological risk factors, the determinants of heterogeneity among patient populations, and the common mediators influencing multiple body systems that are affected in CFS are encouraged. The NIH is interested in funding research that will enhance our knowledge of the disease process and improve the diagnosis, treatment, and quality of life of all persons with CFS.

Background

Chronic fatigue syndrome (CFS) is a debilitating and complex syndrome that involves multiple body systems. It is characterized by profound fatigue that is not improved by bed rest and may be exacerbated or re-kindled by physical or mental activity. Persons with CFS most often function at substantially lower levels of activity from their pre-onset capacities. In addition to these defining characteristics, a diverse array of other symptoms is associated with CFS; these symptoms include cognitive deficits, impaired sleep, myalgia, arthralgia, headache, gastrointestinal symptoms, and tender lymph nodes. Neither a specific cause(s) nor any specific diagnostic test(s) have been identified for this illness. The range of symptoms however, suggests there may be subtle perturbations in multiple physiological pathways that are triggered by diverse causes such as infection, stress, brain structure abnormalities, hormone levels, proinflammatory cytokines, etc. Epidemiological evidence is also limited and requires further study. Existing data suggest however, that CFS occurs 3 to 4 times more frequently among women than among men and 10 times more often in white Americans than in Americans of other racial/ethnic groups. A more recent study disputes these numbers and would narrow the gap between the sexes, as well as, among racial/ethnic population subgroups.

Research Objectives and Experimental Approaches

Well designed studies are needed to provide a better understanding of CFS, prevalence, pathogenesis, and pathophysiology, with the goal of developing improved diagnostic and intervention strategies. The heterogeneity of the CFS population should be recognized in both basic and clinical research; thus sex, age/developmental stage, racial and ethnic variations should be considered along with any subtyping of CFS in the study designs. This PA encourages the integration of basic research with clinical observations. The multisystemic nature of the disease will benefit from a collaborative and multidisciplinary approach. Research within or across scientific disciplines and institutions is encouraged.

Applicants are encouraged to review recommendations from an NIH sponsored CFS science summit held in October 2000 at Arlington, VA. This document may be found at http://www4.od.nih.gov/orwh/cfsWkshopSummary_6-03.pdf. They also are encouraged to review the summary of the scientific workshop: Neuroimmune mechanisms and chronic fatigue syndrome: understanding central mechanisms, which may be found at http://www4.od.nih.gov/orwh/cfs-newhome.html.They also are referred to the “Agenda for Research on Women's Health for the 21st Century, volume 2"(NIH Publication No 99-4386, http://www4.od.nih.gov/orwh/report.pdf), as well as, “Exploring the Biological Contributions to Human Health. Does Sex Matter" (National Academy Press, Washington DC, http://www.nap.edu/, to ensure responsiveness to all aims of this Program Announcement.

Areas of interest where scientific opportunities exist to meet the objectives of this PA cut across many disciplines. They include, but are not limited to:

Epidemiology

- Define the prevalence of the disorder and identify distinct subgroups

- Prospectively study the natural history of incident cases
- Explore whether pathogenesis and pathophysiology differ relative to age, sex, developmental period and racial/ethnic background
- Compare the diagnostic criteria and symptomatology of CFS in children and adolescents with those of adults
- Describe the epidemiology of CFS in older adults and explore the relationship of CFS to general complaints of fatigue and exhaustion in the elderly.
- Conduct case-control comparisons of CFS with syndromes such as fibromyalgia and other multisystemic illnesses that have similar or overlapping symptomatology
- Determine the frequency and severity of sleep restriction or deprivation, excessive daytime sleepiness, altered sleep quality, and primary or secondary sleep disorders including insomnia or hypersomnia

Diagnosis

- Develop/refine objective measures for fatigue or sleepiness and severity of associated sleep disturbances
- Develop/refine technologies to improve the identification and measurement of precipitating factors
- Develop novel and objective biological markers for the diagnosis of CFS
- Develop and validate techniques for linking biomarkers to behavioral responses associated with CFS
- Conduct longitudinal studies and studies with multiple sampling points to capture the progression of CFS symptomatology
- Explore the role of neuroimaging modalities in the diagnosis, treatment and progression of CFS

Risk Factors

- Identify environmental and other precipitants and geographic correlates of CFS
- Conduct animal studies to elucidate the effects of environmental exposures, including endocrine disrupters, on the stress response contributing to CFS.
- Identify the biological antecedent or triggering events that precipitate CFS
- Explore multi-systemic factors as precipitants to CFS symptoms
- Conduct population studies to elucidate potential genetic risk factors

Neurological and Behavioral Factors

- Study the nature of psychiatric comorbidity in CFS patients
- Elucidate the factors/mechanisms mediating cognitive deficits
- Elucidate the factors/mechanisms that elicit chronic pain and inability to sustain physical exertion in CFS patients
- Elucidate the factors/mechanisms involved in altered sleep states, disrupted circadian regulation, or other causes of impaired or ineffective sleep
- Study the relationships between cognitive deficits and sleep disturbances or sleep disorders
- Investigate long term cognitive, psychosocial, and physical health outcomes in children and adolescents with CFS
- Investigate the relationships of fatigue and CFS to other comorbid medical conditions or disabilities common in older patients, and/or to the drug effects and interactions of medications used to treat these conditions

Physiologic Interactions

- Study the role of neuroendocrine and neuroimmune functions in CFS pathogenesis and pathophysiology
- Study the role of neuro-cardiovascular regulation in the loss of the normal control of blood pressure, heart rate and contractility in CFS patients
- Study the action of mediators (i.e., cytokines, chemokines) on the “multiple, interacting, feedback-controlled systems” that are dysregulated in CFS (pathogenesis and pathophysiology)
- Study the mechanisms and consequences of dysregulation in the major physiologic control systems to better understand the multi-system symptoms among CFS patients
- Study the role of oxidative stress in the pathogenesis of and marginal nutritional deficiencies in the etiology of CFS.
- Explore the relationships of fatigue and CFS to elevated levels of inflammatory cytokines (e.g., IL-6) in older patients and to the other components of frailty in the elderly

Treatment and Quality of Life

- Conduct clinical trials in CFS patients to determine the efficacy of reliable and valid strategies that are used to improve quality of life in other chronic diseases

- Conduct definitive trials to determine the effectiveness of currently prescribed pharmacologic, behavioral and other treatments used in CFS
- Develop and test new pharmacologic and nonpharmacologic strategies for ameliorating symptoms that impair quality of life in patients with CFS
- Study perceptions, attitudes, and behaviors that influence both the course of CFS and the quality of care provided to CFS patients
- Examine the role of self-medication with alcohol, and illicit and prescription drugs in CFS patients.
- Examine the use and establish the efficacy and safety of dietary supplements in the treatment of CFS
- Develop and test the efficacy of interventions to ameliorate fatigue and CFS that are targeted at the specific needs of the elderly

Methodological Considerations

Multidisciplinary studies and collaboration among investigators with expertise in appropriate disciplines are encouraged. When investigators are at different institutions, individual R01 applications may include consortium arrangements.

Collaborative arrangements with ongoing studies that provide patient populations, specimens, and data are encouraged. Such arrangements should be clearly delineated in the application.

Investigators are encouraged to use the CFS case definition as presented in Fukuda, et al. Annals of Internal Medicine 1994; 121: 953-9. If other case definitions are proposed, they should be clearly defined and the rationale for the alternative choice clearly delineated. Similar care should be given to definition of sub groupings for CFS patients, if you chose to consider them.

Methods and procedures used in selecting patients or their specimens should be precisely defined and described in detail. Care should be given to the criteria used for case definition and the manner in which the criteria are applied. Similar care should be given to descriptions of procedures and methods for enrolling subjects in comparison groups.

Applications for small studies that explore new ideas or investigative techniques are also encouraged and could provide the basis for submission of a subsequent larger grant application.

The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2010", a PHS-led national activity for setting priority areas. This Program Announcement (PA) is related to several priority areas, including chronic disabling diseases. Potential applicants may obtain a copy of "Healthy People 2010" at http://www.healthypeople.gov/.

Section II. Award Information

1. Mechanism(s) of Support

This funding opportunity will use three NIH award mechanisms: the NIH R01;the R21, Exploratory/Developmental project research grant application http://grants.nih.gov/grants/guide/pa-files/PA-03-107.html; and the R03,small research project grant http://grants.nih.gov/grants/guide/pa-files/PA-03-108.html. As an applicant, you will be solely responsible for planning, directing, and executing the proposed project.

This funding opportunity uses just-in-time concepts. It also uses the modular as well as the non-modular budget formats. (Please see http://grants.nih.gov/grants/funding/modular/modular.htm). Specifically, if you are submitting an application with direct costs in each year of $250,000 or less, use the modular budget format described in the PHS 398 application instructions. Otherwise, follow the instructions for the non-modular research grant applications.

Applicants from institutions that have a General Clinical Research Center (GCRC) funded by the National Center for Research Resources (NCRR) may wish to identify the GCRC as a resource for conducting the proposed research.

2. Funds Available

Although the financial plans of the Institutes involved provide support for this program, awards pursuant to this PA are contingent upon the availability of funds and the receipt of meritorious applications. Because the nature and scope of the proposed research will vary from application to application, it is anticipated that the size and duration of each award will also vary.

Section III. Eligibility Information

1. Eligible Applicants

1.A. Eligible Institutions

You may submit (an) application(s) if your organization has any of the following characteristics:

- For-profit organizations
- Non-profit organizations
- Public or private institutions, such as universities, colleges, hospitals, and laboratories
- Units of State government
- Units of local governments
- Eligible agencies of the Federal government
- Foreign Institutions
- Domestic organizations
- Faith-based or community-based organizations

1.B. Eligible Individuals

Any individual with the skills, knowledge, and resources necessary to carry out the proposed research is invited to work with their institution to develop an application for support. Individuals from underrepresented racial and ethnic groups as well as individuals with disabilities are always encouraged to apply for NIH programs.

2. Cost Sharing

Cost sharing is not required under this program.

3. Other-Special Eligibility Criteria

Not applicable.

Section IV. Application and Submission Information

1. Address to Request Application Information

The PHS 398 application instructions are available at http://grants.nih.gov/grants/funding/phs398/phs398.html in an interactive format. For further assistance contact GrantsInfo, Telephone (301) 435-0714, Email: GrantsInfo@nih.gov.

Telecommunications for the hearing impaired: TTY 301-451-0088.

2. Content and Form of Application Submission

Applications must be prepared using the PHS 398 research grant application instructions and forms. Applications must have a Dun and Bradstreet (D&B) Data Universal Numbering System (DUNS) number as the universal identifier when applying for Federal grants or cooperative agreements. The D&B number can be obtained by calling (866) 705-5711 or through the web site at http://www.dnb.com/us/. The D&B number should be entered on line 11 of the face page of the PHS 398 form.

See also Section VI.2. Administrative Requirements for additional information.

The title and number of this funding opportunity must be typed on line 2 of the face page of the application form and the YES box must be checked.

3. Submission Dates and Times

Applications must be mailed on or before the receipt date described at http://grants.nih.gov/grants/funding/submissionschedule.htm. Submission times N/A.

3.A. Receipt, Review and Anticipated Start Dates

Receipt Dates: http://grants.nih.gov/grants/funding/submissionschedule.htm
Peer Review Date(s): http://grants.nih.gov/grants/funding/submissionschedule.htm
Council Review Date(s): http://grants.nih.gov/grants/funding/submissionschedule.htm
Earliest Anticipated Start Date(s): http://grants.nih.gov/grants/funding/submissionschedule.htm

3.A.1. Letter of Intent

Not applicable.

3.B. Sending an Application to the NIH

Applications must be prepared using the PHS 398 research grant application instructions and forms as described above. Submit a signed, typewritten original of the application, including the checklist, and five signed photocopies in one package to:

Center for Scientific Review
National Institutes of Health
6701 Rockledge Drive, Room 1040, MSC 7710
Bethesda, MD 20892-7710 (U.S. Postal Service Express or regular mail)
Bethesda, MD 20817 (for express/courier service; non-USPS service)

3.C. Application Processing

Applications must be submitted on or before the application receipt dates described above (Section IV.3.A.) and at http://grants.nih.gov/grants/dates.htm.

The NIH will not accept any application in response to this PA that is essentially the same as one currently pending initial review unless the applicant withdraws the pending application. The NIH will not accept any application that is essentially the same as one already reviewed. This does not preclude the submission of a substantial revision of an application already reviewed, but such application must include an Introduction addressing the previous critique.

Although there is no immediate acknowledgement of the receipt of an application, applicants are generally notified of the review and funding assignment within eight (8) weeks.

4. Intergovernmental Review

This initiative is not subject to intergovernmental review.

5. Funding Restrictions

All awards are subject to the terms and conditions, cost principles, and other considerations described in the NIH Grants Policy Statement. The Grants Policy Statement can be found at http://grants.nih.gov/grants/policy/policy.htm (See also Section VI.3. Award Criteria)

6. Other Submission Requirements

Specific Instructions for Modular Grant applications.

Applications requesting up to $250,000 per year in direct costs must be submitted in a modular budget format. The modular budget format simplifies the preparation of the budget in these applications by limiting the level of budgetary detail. Applicants request direct costs in $25,000 modules. Section C of the research grant application instructions for the PHS 398 at http://grants.nih.gov/grants/funding/phs398/phs398.html includes step-by-step guidance for preparing modular budgets. Additional information on modular budgets is available at http://grants.nih.gov/grants/funding/modular/modular.htm. (See also Section II.1. Mechanisms of Support)

Specific Instructions for Applications Requesting $500,000 (direct costs) or More per Year. Applicants requesting $500,000 or more in direct costs for any year must carry out the following steps:

1) Contact the IC program staff at least 6 weeks before submitting the application, i.e., as you are developing plans for the study;

2) Obtain agreement from the IC staff that the IC will accept your application for consideration for award; and,

3) Include a cover letter with the application that identifies the staff member and IC who agreed to accept assignment of the application.

This policy applies to all investigator-initiated new (type 1), competing continuation (type 2), competing supplement, or any amended or revised version of these grant application types. Additional information on this policy is available in the NIH Guide for Grants and Contracts, October 19, 2001 at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-004.html.

Plan for Sharing Research Data

The precise content of the data-sharing plan will vary, depending on the data being collected and how the investigator is planning to share the data. Applicants who are planning to share data may wish to describe briefly the expected schedule for data sharing, the format of the final dataset, the documentation to be provided, whether or not any analytic tools also will be provided, whether or not a data-sharing agreement will be required and, if so, a brief description of such an agreement (including the criteria for deciding who can receive the data and whether or not any conditions will be placed on their use), and the mode of data sharing (e.g., under their own auspices by mailing a disk or posting data on their institutional or personal website, through a data archive or enclave). Investigators choosing to share under their own auspices may wish to enter into a data-sharing agreement. References to data sharing may also be appropriate in other sections of the application.

All applicants must include a plan for sharing research data in their application. The data sharing policy is available at http://grants.nih.gov/grants/policy/data_sharing. All investigators responding to this funding opportunity should include a description of how final research data will be shared, or explain why data sharing is not possible.

The reasonableness of the data sharing plan or the rationale for not sharing research data will be assessed by the reviewers. However, reviewers will not factor the proposed data sharing plan into the determination of scientific merit or the priority score.

Sharing Research Resources

NIH policy requires that grant awardee recipients make unique research resources readily available for research purposes to qualified individuals within the scientific community after publication (see NIH Grants Policy Statement http://grants.nih.gov/grants/policy/nihgps and http://ott.od.nih.gov/newpages/rtguide_final.html). Investigators responding to this funding opportunity should include a plan for sharing research resources addressing how unique research resources will be shared or explain why sharing is not possible.

The adequacy of the data sharing plan and the resources sharing plan will be considered by Program staff of the funding organization when making recommendations about funding applications. The effectiveness of the resource sharing will be evaluated as part of the administrative review of each non-competing Grant Progress Report. (PHS 2590). See Section VI.3. Award Criteria.

Section V. Application Review Information

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1. Criteria

Not applicable.

2. Review and Selection Process

Applications submitted for this funding opportunity will be assigned to the ICs on the basis of established PHS referral guidelines.

Appropriate scientific review groups convened in accordance with the standard NIH peer review procedures (http://www.csr.nih.gov/refrev.htm) will evaluate applications for scientific and technical merit.

As part of the initial merit review, all applications will:

- Undergo a selection process in which only those applications deemed to have the highest scientific merit, generally the top half of applications under review, will be discussed and assigned a priority score.
- Receive a written critique

- Receive a second level of review by the appropriate national advisory councils or boards

3. Merit Review Criteria

The goals of NIH supported research are to advance our understanding of biological systems, to improve the control of disease, and to enhance health. In their written critiques, reviewers will be asked to comment on each of the following criteria in order to judge the likelihood that the proposed research will have a substantial impact on the pursuit of these goals. Each of these criteria will be addressed and considered in assigning the overall score, weighting them as appropriate for each application. Note that an application does not need to be strong in all categories to be judged likely to have major scientific impact and thus deserve a high priority score. For example, an investigator may propose to carry out important work that by its nature is not innovative but is essential to move a field forward.

1. Significance. Does this study address an important problem? If the aims of the application are achieved, how will scientific knowledge or clinical practice be advanced? What will be the effect of these studies on the concepts, methods, technologies, treatments, services, or preventative interventions that drive this field?

2. Approach. Are the conceptual or clinical framework, design, methods, and analyses adequately developed, well integrated, well reasoned, and appropriate to the aims of the project? Does the applicant acknowledge potential problem areas and consider alternative tactics?

3. Innovation. Is the project original and innovative? For example: Does the project challenge existing paradigms or clinical practice; address an innovative hypothesis or critical barrier to progress in the field? Does the project develop or employ novel concepts, approaches, methodologies, tools, or technologies for this area?

4. Investigators. Are the investigators appropriately trained and well suited to carry out this work? Is the work proposed appropriate to the experience level of the principal investigator and other researchers? Does the investigative team bring complementary and integrated expertise to the project (if applicable)?

5. Environment. Does the scientific environment in which the work will be done contribute to the probability of success? Do the proposed studies benefit from unique features of the scientific environment, or subject populations, or employ useful collaborative arrangements? Is there evidence of institutional support?

3.A. Additional Review Criteria:

In addition to the above criteria, the following items will be considered in the determination of scientific merit and the priority score:

Protection of Human Subjects from Research Risk: The involvement of human subjects and protections from research risk relating to their participation in the proposed research will be assessed (see the Research Plan, Section E on Human Subjects in the PHS Form 398).

Inclusion of Women, Minorities and Children in Research: The adequacy of plans to include subjects from both genders, all racial and ethnic groups (and subgroups), and children as appropriate for the scientific goals of the research will be assessed. Plans for the recruitment and retention of subjects will also be evaluated (see the Research Plan, Section E on Human Subjects in the PHS Form 398).

Care and Use of Vertebrate Animals in Research: If vertebrate animals are to be used in the project, the five items described under Section F of the PHS Form 398 research grant application instructions will be assessed.

3.B. Additional Review Considerations

Budget: The reasonableness of the proposed budget and the requested period of support in relation to the proposed research. The priority score should not be affected by the evaluation of the budget.

3.C. Sharing Research Data

1. **Data Sharing Plan:** The reasonableness of the data sharing plan or the rationale for not sharing research data **will** be assessed by the reviewers. However, reviewers will not factor the proposed data sharing plan into the determination of scientific merit or the priority score. The presence of a data sharing plan will be part of the terms and conditions of the award. The funding organization will be responsible for monitoring the data sharing policy.

3.D. Sharing Research Resources

NIH policy requires that grant awardee recipients make unique research resources readily available for research purposes to qualified individuals within the scientific community after publication (see NIH Grants Policy Statement http://grants.nih.gov/grants/policy/nihgps_2003/index.htm and http://ott.od.nih.gov/newpages/rtguide_final.html). Investigators responding to this funding opportunity should include a sharing research resources plan addressing how unique research resources will be shared or explain why sharing is not possible.

The adequacy of the resources sharing plan will be considered by Program staff of the funding organization when making recommendations about funding applications. Program staff may negotiate modifications of the data and resource sharing plans with the Principal Investigator before recommending funding of an application. The final version of the data and resource sharing plans negotiated by both will become a condition of the award of the grant. The effectiveness of the resource sharing will be evaluated as part of the administrative review of each non-competing Grant Progress Report. (PHS 2590). See Section VI.3. Award Criteria.

Section VI. Award Administration Information

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1. Award Notices

After the peer review of the application is completed, the Principal Investigator will also receive a written critique called a summary statement.

If the application is under consideration for funding, NIH will request "just-in-time" information from the applicant. For details, applicants may refer to the NIH Grants Policy Statement Part II: Terms and Conditions of NIH Grant Awards, Subpart A: General http://grants.nih.gov/grants/policy/nihgps_2003/NIHGPS_part4.htm.

A formal notification in the form of a Notice of Grant Award (NGA) will be provided to the applicant organization. The NGA signed by the grants management officer is the authorizing document.

Selection of an application for award is not an authorization to begin performance. Any costs incurred before receipt of the NGA (Notice of Grant Award) are at the recipient's risk. These costs may be reimbursed only to the extent considered allowable pre-award costs.

Each IC will transmit this NGA through either postal or electronic means, or both, in accordance with its standard procedure.

2. Administrative and National Policy Requirements

All NIH Grant and cooperative agreement awards include the NIH Grants Policy Statement as part of the notice of grant award. For these terms of award, see the NIH Grants Policy Statement Part II: Terms and Conditions of NIH Grant Awards, Subpart A: General http://grants.nih.gov/grants/policy/nihgps_2003/NIHGPS_Part4.htm and Part II Terms and Conditions of NIH Grant Awards, Subpart B: Terms and Conditions for Specific Types of Grants, Grantees, and Activities http://grants.nih.gov/grants/policy/nihgps_2003/NIHGPS_part9.htm.

The following Terms and Conditions will be incorporated into the award statement and will be provided to the Principal Investigator as well as to the appropriate institutional official, at the time of award.

3. Award Criteria

The following will be considered in making funding decisions:

- Scientific merit of the proposed project as determined by peer review
- Availability of funds
- Relevance of program priorities

4. Reporting

Awardees will be required to submit the PHS Non-Competing Grant Progress Report, Form 2590 annually: http://grants.nih.gov/grants/funding/2590/2590.htm and financial statements as required in the NIH Grants Policy Statement.

Section VII. Agency Contacts

We encourage your inquiries concerning this funding opportunity and welcome the opportunity to answer questions from potential applicants. Inquiries may fall into three areas: scientific/research, peer review, and financial or grants management issues:

1. Scientific/Research Contacts:

Office of Research on Women's Health (ORWH)
Dr. Eleanor Hanna
Associate Director for Special Projects and Centers
Office for Research on Women's Health
National Institutes of Health Shannon Building, Room 201
Bethesda, MD 20892
Phone: (301) 402-1770
Email: HannaE@od.nih.gov

Office of Behavioral and Social Science Research (OBSSR)
Dr. Susan Solomon
Senior Advisor
National Institutes of Health Shannon Building, Room 256
Bethesda, MD 20892
Phone: (301) 496-0979
Email: Ssolomon@nih.gov

Office of Dietary Supplements (ODS)
The ODS supports studies that further understanding of the biochemical and cellular effects of dietary supplements and their physiological impact across the life cycle. Specifically how dietary supplements moderate, alter, or enhance metabolic, physiological, and psychological processes associated with maintenance or lack of optimal health and performance.

Dr. Rebecca B. Costello Deputy Director
Office of Dietary Supplements
National Institutes of Health 31 Center Drive, Room 1B29
Bethesda, MD 20892-2086
Phone: (301) 435-2920
Email: CostellB@od.nih.gov

National Heart, Lung, Blood Institute (NHLBI)
Dr. Stephen S. Goldman
National Heart, Lung, Blood Institute, NIH
6701 Rockledge Drive, Suite 10193, MSC 7956
Bethesda, MD 20892-7920
Phone: 301-435-0560
Email: goldmans@nhlbi.nih.gov

Dr. Carl E. Hunt Director
National Center on Sleep Disorders Research
National Heart, Lung, Blood Institute, NIH
6705 Rockledge Drive, Suite 6022
Bethesda, MD 20892-7993
Phone: 301-435-0199
Email: huntc@nhlbi.nih.gov

National Institute on Alcohol Abuse and Alcoholism (NIAAA)
The National Institute on Alcohol Abuse and Alcoholism (NIAAA) accepts applications on alcohol health effects that are co-morbid with chronic fatigue syndrome. The NIAAA accepts applications if they have explicit relevance to Alcohol as reflected in the title, abstract, theoretical framework, specific aims, measures and analyses. For more information and pre-application technical assistance, please contact:

Dr. Denise Russo
National Institute on Alcohol Abuse and Alcoholism/NIH
Division of Metabolism and Health Effects
5635 Fishers Lane, Room 2037
Bethesda, MD 20892-9304
Phone: 301-402-9403, Fax: 301-594-0673
Email: drusso@mail.nih.gov

National Institute of Allergy and Infectious Diseases (NIAID)
Dr. David Morens
National Institute of Allergy and Infectious Diseases/NIH
6700B Rockledge Drive Room 3258
Bethesda, MD 20892-7630
Phone: (301) 402-8652
Email: dmorens@niaid.nih.gov

Dr. Thomas Esch
Clinical Immunology Branch, DAIT
National Institute of Allergy and Infectious Diseases/NIH
6610 Rockledge Drive Room 3022
Bethesda, MD 20892-6601
Phone: (301) 496-7104
Email: te51h@nih.gov

National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)
The National Institute of Arthritis and Musculoskeletal and Skin Diseases accepts applications on chronic fatigue syndrome that is comorbid with fibromyalgia syndrome (FMS), applications comparing CFS patients with FMS patients, or other CFS applications with explicit relevance to FMS or other rheumatic disorders. T he NIAMS will not accept R03 applications in response to this PA.

Dr. Deborah N. Ader
National Institute of Arthritis and Musculoskeletal and Skin Diseases/NIH
6701 Democracy Blvd., Suite 800
Bethesda, MD 20892
Phone: (301) 594-5032
Email: aderd@mail.nih.gov

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National Institute of Environmental Health Science (NIEHS)
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National Institute of Nursing Research (NINR)
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National Institute of Mental Health (NIMH)
Although not a formal sponsor of this program announcement, NIMH accepts applications on mental health disorders that are

co-morbid with chronic fatigue syndrome. The NIMH accepts applications if they have explicit relevance to mental disorders, symptoms, or related disability as reflected in the title, abstract, theoretical framework, specific aims, measures and analyses. For more information and pre-application technical assistance, please contact:

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National Institute on Mental Health,
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National Institute of Neurological Disorders and Stroke (NINDS)
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National Institute of Dental and Craniofacial Research (NIDCR)
The NIDCR supports research on Chronic Fatigue Syndrome (CFS) to the extent that many of the symptoms of CFS overlap with temporomandibular joint disorder (TMJD). For example, patients with TMJD often present with pain in areas other than the TMJ, and in common with pain exhibited in CFS patients. Research aimed at uncovering and elucidating the biological mechanisms underlying the overlapping symptoms found in TMJ and of CFS is of particular interest.

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National Institute on Aging (NIA)
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2. Peer Review Contacts:

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3. Financial or Grants Management Contacts:

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Section VIII. Other Information

Required Federal Citations

Use of Animals in Research:
Recipients of PHS support for activated involving live, vertebrate animals must comply with PHS Policy on Humane Care and Use of Laboratory Animals (http://grants.nih.gov/grants/olaw/references/PHSPolicyLabAnimals.pdf), as mandated by the Health Research Extension Act of 1985 (http://grants.nih.gov/grants/olaw/references/hrea1985.htm), and the USDA Animal Welfare Regulations (http://www.nal.usda.gov/awic/legislat/usdaleg1.htm), as applicable.

Human Subjects Protection:
Federal regulations (45CFR46) require that applications and proposals involving human subjects must be evaluated with reference to the risks to the subjects, the adequacy of protection against these risks, the potential benefits of the research to the subjects and others, and the importance of the knowledge gained or to be gained, http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm.

Data and Safety Monitoring Plan:
Data and safety monitoring is required for all types of clinical trials, including physiologic toxicity, and dose-finding studies (phase I); efficacy studies (Phase II) efficacy, effectiveness and comparative trials (Phase III). Monitoring should be commensurate with risk. The establishment of data and safety monitoring boards (DSMBs) is required for multi-site clinical trials involving interventions that entail potential risks to the participants. (NIH Policy for Data and Safety Monitoring, NIH Guide for Grants and Contracts, June 12, 1998: http://grants.nih.gov/grants/guide/notice-files/not98-084.html).

Sharing Research Data:
Investigators submitting an NIH application seeking $500,000 or more in direct costs in any single year are expected to include a plan for data sharing or state why this is not possible. http://grants.nih.gov/grants/policy/data_sharing

Investigators should seek guidance from their institutions on issues related to institutional policies, local IRB rules, as well as local, State and Federal laws and regulations, including the Privacy Rule. Reviewers will consider the data sharing plan but will not factor the plan into the determination of the scientific merit or the priority score.

Sharing of Model Organisms:
NIH is committed to support efforts that encourage sharing of important research resources including the sharing of model organisms for biomedical research (see http://grants.nih.gov/grants/guide/notice-files/NOT-OD-04-042.html). At the same time the NIH recognizes the rights of grantees and contractors to elect and retain title to subject inventions developed with Federal funding pursuant to the Bayh Dole Act (see the NIH Grants Policy Statement http://grants.nih.gov/grants/policy/nihgps_2003/index.htm). All investigators submitting an NIH application or contract proposal beginning with the October 1, 2004 receipt date, are expected to include in the application/proposal a description of a specific plan for sharing and distributing unique model organism research resources generated using NIH funding or state why such sharing is restricted or not possible. This will permit other researchers to benefit from the resources developed with public funding. The inclusion of a model organism sharing plan is not subject to a cost threshold in any year and is expected to be included in all applications where the development of model organisms is anticipated.

Inclusion of Women And Minorities in Clinical Research:
It is the policy of the NIH that women and members of minority groups and their sub-populations must be included in all NIH-supported clinical research projects unless a clear and compelling justification is provided indicating that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. This policy results from the NIH Revitalization Act of 1993 (Section 492B of Public Law 103-43). All investigators proposing clinical research should read the "NIH Guidelines for Inclusion of Women and Minorities as Subjects in Clinical Research (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-001.html); a complete copy of the updated Guidelines is available at http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm. The amended policy incorporates: the use of an NIH definition of clinical research; updated racial and ethnic categories in compliance with the new OMB standards; clarification of language governing NIH-defined Phase III clinical trials consistent with the new PHS Form 398; and updated roles and responsibilities of NIH staff and the extramural community. The policy continues to require for all NIH-defined Phase III clinical trials that: a) all applications or proposals and/or protocols must provide a description of plans to conduct analyses, as appropriate, to address differences by sex/gender and/or racial/ethnic groups, including subgroups if applicable; and b) investigators must report annual accrual and progress in conducting analyses, as appropriate, by sex/gender and/or racial/ethnic group differences.

Inclusion of Children as Participants in Clinical Research:
The NIH maintains a policy that children (i.e., individuals under the age of 21) must be included in all clinical research, conducted or supported by the NIH, unless there are scientific and ethical reasons not to include them.

All investigators proposing research involving human subjects should read the "NIH Policy and Guidelines" on the inclusion of children as participants in research involving human subjects that is available at http://grants.nih.gov/grants/funding/children/children.htm.

Required Education on the Protection of Human Subject Participants:
NIH policy requires education on the protection of human subject participants for all investigators submitting NIH applications for research involving human subjects and individuals designated as key personnel. The policy is available at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html.

Human Embryonic Stem Cells (hESC):
Criteria for federal funding of research on hESCs can be found at http://stemcells.nih.gov/index.asp and at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-005.html. Only research using hESC lines that are registered in the NIH Human Embryonic Stem Cell Registry will be eligible for Federal funding (see http://escr.nih.gov/) It is the responsibility of the applicant to provide in the project description and elsewhere in the application as appropriate, the official NIH identifier(s) for the hESC line(s)to be used in the proposed research. Applications that do not provide this information will be returned without review.

Public Access to Research Data through the Freedom of Information Act:
The Office of Management and Budget (OMB) Circular A-110 has been revised to provide public access to research data through the Freedom of Information Act (FOIA) under some circumstances. Data that are (1) first produced in a project that is supported in whole or in part with Federal funds and (2) cited publicly and officially by a Federal agency in support of an action that has the force and effect of law (i.e., a regulation) may be accessed through FOIA. It is important for applicants to understand the basic scope of this amendment. NIH has provided guidance at http://grants.nih.gov/grants/policy/a110/a110_guidance_dec1999.htm. Applicants may wish to place data collected under this PA in a public archive, which can provide protections for the data and manage the distribution for an indefinite period of time. If so, the application should include a description of the archiving plan in the study design and include information about this in the budget justification section of the application. In addition, applicants should think about how to structure informed consent statements and other human subjects procedures given the potential for wider use of data collected under this award.

Standards for Privacy of Individually Identifiable Health Information:
The Department of Health and Human Services (DHHS) issued final modification to the "Standards for Privacy of Individually Identifiable Health Information," the "Privacy Rule," on August 14, 2002. The Privacy Rule is a federal regulation under the Health Insurance Portability and Accountability Act (HIPAA) of 1996 that governs the protection of individually identifiable health information, and is administered and enforced by the DHHS Office for Civil Rights (OCR).

Decisions about applicability and implementation of the Privacy Rule reside with the researcher and his/her institution. The OCR website (http://www.hhs.gov/ocr/) provides information on the Privacy Rule, including a complete Regulation Text and a set of decision tools on "Am I a covered entity?" Information on the impact of the HIPAA Privacy Rule on NIH processes involving the review, funding, and progress monitoring of grants, cooperative agreements, and research contracts can be found at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-03-025.html.

URLs in NIH Grant Applications or Appendices:
All applications and proposals for NIH funding must be self-contained within specified page limitations. Unless otherwise specified in an NIH solicitation, Internet addresses (URLs) should not be used to provide information necessary to the review because reviewers are under no obligation to view the Internet sites. Furthermore, we caution reviewers that their anonymity may be compromised when they directly access an Internet site.

Healthy People 2010:
The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2010," a PHS-led national activity for setting priority areas. This PA is related to one or more of the priority areas. Potential applicants may obtain a copy of "Healthy People 2010" at http://www.healthypeople.gov/.

Authority and Regulations:
This program is described in the Catalog of Federal Domestic Assistance at http://www.cfda.gov/ and is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review. Awards are made under the authorization of Sections 301 and 405 of the Public Health Service Act as amended (42 USC 241 and 284) and under Federal Regulations 42 CFR 52 and 45 CFR Parts 74 and 92. All awards are subject to the terms and conditions, cost principles, and other considerations described in the NIH Grants Policy Statement. The NIH Grants Policy Statement can be found at http://grants.nih.gov/grants/policy/policy.htm. The Office of Dietary Supplements (ODS) was established in 1994 under the Dietary Supplement Health and Education Act (DSHEA), Public Law 103-417, Section 3a to establish standards with respect to dietary supplements.

The PHS strongly encourages all grant recipients to provide a smoke-free workplace and discourage the use of all tobacco products. In addition, Public Law 103-227, the Pro-Children Act of 1994, prohibits smoking in certain facilities (or in some cases, any portion of a facility) in which regular or routine education, library, day care, health care, or early childhood development services are provided to children. This is consistent with the PHS mission to protect and advance the physical and mental health of the American people.

Weekly TOC for this Announcement
NIH Funding Opportunities and Notices

Department of Health
and Human Services

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